REMARKS

Claims 1, 3, 5-29, and 76 constitute the pending claims in the present application. Among them, claims 29 and 76 are directed to non-elected inventions and are withdrawn from further consideration. Applicants will cancel these claims upon indication of allowable subject matter. Claim 5 is also withdrawn from further consideration as being directed to non-elected species of the elected Group I invention. Currently, claims 1, 3, and 6-29 are under consideration.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Specification

The Office Action objects to the specification under 35 USC 132 for introducing new matter. Specifically, the Office Action asserts that the term "non-neuronal" does not appear to be in the originally filed specification, and request cancellation of the alleged new matter.

To expedite prosecution, Applicants have amended claims 1, 3, 6, and 7 to obviate this objection. Reconsideration and withdrawal of the objection is respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 1, 3, 6, 8-22, and 28 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. Specifically, the Office Action asserts that the term "non-neuronal" does not appear to be in the originally filed specification.

To expedite prosecution, Applicants have amended claims 1, 3, 6, and 7 to obviate this rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 3, and 8-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for methods of screening for BMP-related factors, does not reasonably provide enablement for screens for morphogens as broadly claimed. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Specifically, the Office Action asserts that "Applicants indicates that 'morphogens' encompasses members of the TGF-beta superfamily. However, the art teaches that TGF-beta itself is implicated in kidney disease. See, for example, Kumar *et al.*, ... Kumar *et al.* suggests blocking TGF-beta as a means of treating kidney disease (p.F838, column 1). Thus one of skill in the art could not predictably use Applicants' invention as broadly claimed to identify and assess morphogens as broadly claimed."

Applicants submit that the rejection likely stems from the misinterpretation of the term "morphogen" as described in the specification, which does not include TGF-beta.

The specification describes, in several different occasions, that a "morphogen" or "morphogenic protein" or "osteogenic protein" includes the BMP subfamily of the TGF-beta superfamily. According to these definitions, TGF-beta would not be a member of such BMP proteins. For example, the specification describes on page 1, first paragraph under "Background of the Invention" that:

> "[a] class of proteins now has been identified that is competent to act as true tissue morphogens. That is, these proteins are able, on their own, to induce the migration, proliferation and differentiation of progenitor cells into functional replacement tissue. This class of proteins, referred to herein as 'osteogenic proteins' or 'morphogenic proteins' or 'morphogens,' includes members of the family of bone morphogenetic proteins (BMPs) identified by their ability to induce ectopic, endochondral bone morphogenesis. The morphogenic proteins generally are classified in the art as a subgroup of the TGF-P superfamily of growth factors (Hogan (1996) Genes & Development 10: 1580-1594). Members of the morphogen family of proteins include the mammalian osteogenic protein-I (OP- 1, also known as BMP-7, and the Drosophila homolog 60A), osteogenic protein-2 (OP-2, also known as BMP-8), osteogenic protein-3 (OP-3), BMP-2 (also known as BMP-2A or CBMP-2A, and the Drosophila homolog DPP), BMP-3, BMP-4 (also known as BMP-2B or CBMP-2B), BMP-5, BMP-6 and its murine homolog Vgr-1, BMP-9, BMP-10, BMP-11, BMP-12, GDF3 (also known as Vgr2), GDF8, GDF9, GDF10, GDF11, GDF12, BMP-13, BMP-14, BMP-15, GDF-5 (also known as CDMP-1 or MP52), GDF-6 (also known as CDMP-2), GDF-7 (also known as CDMP-3), the Xenopus homolog Vg1 and NODAL, UNIVIN, SCREW, ADMP, and NEURAL.
>
> Members of this family encode secreted polypeptide chains sharing common structural features, including processing from a precursor 'pro-form to yield a mature polypeptide chain competent to dimerize and containing a carboxy terminal active domain, of approximately 97-106 amino acids. All members

> share a conserved pattern of cysteines in this domain and the active form of these proteins can be either a disulfide-bonded homodimer of a single family member or a heterodimer of two different members (see, e.g., Massague (1990) Annu. Rev. Cell Biol. 6:597...). These disclosures describe the amino acid and DNA sequences, as well as the chemical and physical characteristics, of these osteogenic proteins. See also, Wozney *et al.* (1988) Science 242:1528-1534)...

Similar description can also be found on page 7, second paragraph, to page 8, first paragraph; and again on page 12, first paragraph.

In contrast, TGF-beta was not known in the art as a "morphogen," at least not as defined in the instant specification. In fact, neither the instant specification nor the cited reference refer to TGF-beta as a "morphogen" or "morphogenic protein." The specification (as published in WO 98/54572) actually refers to TGF-beta as a "growth factor" on page 5, line 27. The confusion likely results, at least partly, from the term "TGF-beta superfamily," which includes all the BMP family of morphogens, the TGF-beta proteins (not morphogen), activins, inhibins, MIS (Mullerian-inhibiting substance) (see Heldin *et al.*, *Nature* **390**: 465-471, **Exhibit A**, especially the first paragraph). These TGF-beta superfamily proteins use largely distinct intracellular signaling pathways, and exhibit a diverse array of biological functions. The term "morphogen" is reserved for the BMP subfamily of proteins within the TGF-beta superfamily, but does not encompass the other members of the TGF-beta superfamily.

Since the Office Action acknowledges that the claimed invention is enabled for the BMP-related factors, Applicants submit that the claimed invention is enabled to the full scope. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 112, second paragraph

Claims 1, 3, 6, and 8-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action asserts that the term "analog" is not defined in the specification, and one of skill in the art would not know what molecules were encompassed.

The specification describes on page 12, last paragraph that "[i]n general terms, an 'analog' is understood to be a functional equivalent of a given substance and can be a substitute for said substance, including as a therapeutic substitute. An analog also can be a structural equivalent. As used herein, a 'morphogen analog' is a substance that mimics a biological effect induced and/or mediated by a morphogen, such as OP-1. Any substance having such mimetic properties, regardless of the chemical or biochemical nature thereof, can be used as a morphogen analog herein. A morphogen analog as contemplated herein can be a simple or complex substance produced by a living system or through chemical or biochemical synthetic techniques. It can be a substance that occurs in nature or it can be a novel substance, e.g., prepared according to principles of rational drug design. It can be a substance that structurally resembles a solvent-exposed morphogen surface epitope implicated in receptor interactions, a substance that otherwise stimulates a morphogen receptor displayed on the surface of a morphogen responsive cell, or a cell-membrane permeant substance or otherwise intracellular-acting molecule that interacts with an intracellular component of the signal transduction machinery of a morphogen-responsive cell and thereby stimulates a morphogen specific biological effect. Such intracellular acting morphogen analogs also are referred to herein as 'downstream morphogenesis inducers.' As used herein, a morphogen analog can be referred to as a 'mimic' or a 'mimetic.'" The following 2-3 pages further elaborate "analog" by describing several embodiments of the envisioned analogs.

The specification further describes "analog" as encompassing "candidate non-protein-based 'small molecule' functional mimetics" (page 3, lines 4-5). It also describes "morphogen analog" as "any candidate compound competent to induce a morphogen-mediated biological effect... include homologs and ligand analogs that can substitute for a morphogen in a ligand-morphogen receptor binding interaction, as well as functional mimetics competent to induce biological effect of morphogenesis by inducing a downstream effect normally stimulated by ligand-morphogen receptor binding under native conditions." (page 8, lines 10-15)

Therefore, the term "analog" is well-defined in the instant specification. A skilled artisan would have no problem determining what molecules are encompassed by the term without undue experimentation. Thus reconsideration and withdrawal of the rejection are respectfully requested.

Claims 23 and 25 are rejected as being indefinite, since the term "variants" is allegedly not defined, and a skilled artisan would not know what degree of alteration would be considered a variation.

Applicants submit that the term "variant" is also well-described in the instant specification. For example, page 7, last paragraph describes that "[i]n one preferred embodiment, the proteins useful in the invention include biologically active species variants of any of these proteins, including conservative amino acid sequence variants, proteins encoded by degenerate nucleotide sequence variants, and osteogenically active proteins sharing the conserved seven cysteine skeleton as defined herein and encoded by a DNA sequence competent to hybridize to a DNA sequence encoding a morphogenic protein disclosed herein, including, without limitation, OP-1, BMP-5, BMP-6, BMP-2, BMP-4 or GDF-5, GDF-6 or GDF7." Similar language is also found on page 12, 1st paragraph; and page 22, last full paragraph. Furthermore, the specification describes on page 25, lines 15-19, that "[t]he term 'conservative variant' or 'conservative variation' also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid in a given polypeptide chain, provided that antibodies having binding specificity for the resulting substituted polypeptide chain also have binding specificity (i.e., 'crossreact' or 'immunoreact' with) the unsubstituted or parent polypeptide chain." The paragraph immediately above the recited passage describes what kind of substitution is considered "conserved," citing the authoritative Dayhoff reference.

Therefore, Applicants submit that the term "variant" is also well-defined in the instant specification. A skilled artisan would not have problem determining what molecules are encompassed by the term. Thus reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 102(b)

Claims 1, 6, 12-15, 20, and 23-28 are rejected under 35 U.S.C. 102(b), as being anticipated by Kuberasampath *et al.*, WO 93/04692.

Specifically, the Office Action alleges that Kuberasampath teaches models for evaluating morphogens *in vivo* in surgically-induced renal ischemia-reperfusion injury, followed by parental

administration of the morphogen. The Office Action also alleges that intravenous administration is taught in a cardiac model on page 70 and 73, anticipating claim 13; and that oral administration is taught on page 81, anticipating claim 14.

Applicants submit that there is a subtle, yet fundamentally important difference between the claimed invention and the disclosure of WO 93/04692. The claimed invention is a *screening method* aimed at identifying, from amongst a list of candidate morphogens or analogs thereof, morphogens / analogs that perform at a comparable level as a control (as recited in step 1(d)), which is known to be a functional morphogen. One purpose of the claimed invention is to fill the need, as the instant specification puts it on page 3, 1st paragraph, to (A) improve "means for evaluating the *in vivo* activity and/or efficacy of these morphogenic proteins and analogs thereof," since "[i]t is anticipated that different morphogens will have differing specific activities for effecting morphogenesis in a given tissue or organ"; (B) to evaluate morphogen analogs / mimetics "for their ability to functionally substitute for a given morphogen *in vivo*"; (C) to evaluate "the pharmacokinetics of a morphogenic protein or analog thereof, including evaluating dosing, preferred administration times, and preferred administration routes for administering a given morphogen, and/or analog to a given individual, for different therapeutic applications." For example, for any given or chosen use, such as using OP-1 to treat a renal disease, there may be a need to substitute OP-1 with a different morphogen or morphogen analog. In that case, the claimed invention would provide a screen method to identify, amongst a list of candidates, morphogens / analogs that would perform substantially the same as OP-1 (control) in that specific use.

In contrast, WO 93/04692 describes a *treatment method* using morphogens that happen to overlap in scope to the subject morphogens of the claimed invention. In certain situations, when it is not certain if a given morphogen would indeed perform a desired function in a disease condition, WO 93/04692 suggests that the effect of that morphogen on that disease condition can be tested by comparing it to an untreated control, which by definition, does not perform a function (as required in step 1(d)) to the disease condition. For example, according to the disclosure of WO93/04692, if a skilled artisan is not certain if OP-1 can treat a renal disease, then the artisan could test it in one of the disclosed animal models by comparing the effect of OP-1 vs. a control vehicle (negative control) on that renal disease. In addition, WO 93/04692 is

completely silent about "morphogen analog" or "variants" within the meaning of the claimed invention.

Thus, the claimed invention is a screening method aimed at identifying a suitable morphogen / analog that performs the same function as the control, while the disclosed method in WO 93/04692 is a test method aimed at determining if a given morphogen performs a certain desired function that the control does not perform. Thus WO 93/04692 cannot anticipate the claimed invention, because it fails to teach or suggest all the limitations of the claimed invention. The same argument also applies to all the dependent claims of claim 1.

Therefore, all amended claims are novel over Kuberasampath *et al.*, and Kuberasampath cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 103(a)

Claims 8-11, 21, and 22 are rejected under 35 U.S.C. 103(a), as being obvious in view of WO 93/04692. Specifically, the Office Action asserts that although WO 93/04692 "fails to teach dosage optimization, as claimed in claim 3, or evaluation in compromised animals as claimed in claims 8-11, 21, and 22, ... it would have been obvious to one of ordinary skill to evaluate treatment parameters such as time of administration and administration to compromised animals." The Office Action asserts that optimization of treatment protocols are standard, as taught in Benet and Sheiner (or "Benet"), which allegedly includes age and disease as affecting drug administration.

Pursuant to MPEP 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

As argued above, the claimed invention in claims 1 and 3 (and their dependent claims 8-11, 21, and 22) is directed to a screening method and relies on comparing results with a positive control, while WO 93/04692 describes a method for testing the potential function of morphogens in tissues / disease conditions, which method relies on comparing results with a negative control. Benet, even combined with WO 93/04692, does not eliminate this gap. Thus the combined teaching of the prior art still fails to teach or suggest all the limitations of the claimed invention, and a skilled artisan would have had no reasonable expectation of success at arriving at the claimed invention. Thus all requirements for establishing a *prima facie* case of obviousness are not met. Reconsideration and withdrawal of the rejection are respectfully requested.

Furthermore, Applicants submit that claims 8-11, 21, and 22 are all dependent claims of claims 1 or 3, which are directed to specific subsets of mammals, such as aged (claim 8), with a reduced capacity to induce callus formation (claim 9), afflicted with impaired blood flow to the skeletal extremities (claim 10), with a reduced capacity to induce an endogenous morphogenetic signal (claim 11), steroidal drug user (claim 21), or aged, obese, hypertensive, or afflicted with osteopenia or diabetes (claim 22). The instant specification teaches in Example 7 that systemic administration resulted in a faster callus and bone formation in older rats as compared with controls (page 48, second paragraph). This result suggests that, in older (aged, with reduced capacity to induce callus formation, etc.) animals, the effects of the systemically administered morphogens are more pronounced than in younger animals. Thus it would be easier to evaluate the morphogenic activity in such older animals.

On the contrary, Applicants submit that WO 93/04692 is completely silent about the advantage or disadvantage of using <u>older</u> (rather than younger) mammals for the claimed screen method.

Even assuming, for the sake of argument, that a skilled artisan would have been motivated to combine WO 93/04692 with Benet, the artisan might at best consider age as one potential factor when evaluating the claimed method in a mammal. However, the artisan would have had no predisposition as to which mammal (older vs. younger) to use for the claimed invention, since it is not taught or suggested in the cited references, separately or in combination, whether an older or younger mammal would have been advantageous. In other words, the

combined teaching of the prior art would still fail to teach or suggest *all the limitations* of the claimed invention. It naturally follows that a skilled artisan would have had *no reasonable expectation of success* to arrive at the claimed invention in view of the teachings of the prior art.

Similarly, Benet at best suggests that certain disease states may affect drug availability, half-life, clearance, and volume of distribution *in vivo*. However, the combined teachings (even if there is motivation to combine) suggest nothing about the specific disease conditions recited in the rejected claims. It may be true that the disease condition of a mammal to be treated could generally have an effect on drug administration. However, different disease conditions most likely would have different effects on the efficacy of any particular drug. For example, a kidney disease might have a substantial effect on, for example, the efficacy of a morphogen, while a heart disease might have minimal, if any, effect on the efficacy of that morphogen. Since there may be numerous candidate disease conditions for a skilled artisan to consider when administering the subject morphogen or its analog, the skilled artisan would simply have had no notion as to whether a specific disease condition would affect the outcome of the claimed method. In other words, the combined teaching of the prior art would still fail to teach or suggest *all the limitations* of the claimed invention. It naturally follows that a skilled artisan would have had *no reasonable expectation of success* to arrive at the claimed invention in view of the teaching of the prior art.

Thus, in view of the foregoing, all of the three basic requirements of a *prima facie* case of obviousness are not met. Applicants submit that all pending claims are non-obvious in view of the cited references or combination thereof. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims as amended are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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